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Abstract	<i>Purpose:</i>	This study was designed to determine the role of laparoscopic adrenalectomy (LA) in the surgical management of adrenocortical carcinoma (ACC).
	<i>Methods:</i>	A systematic literature review was performed on January 2, 2015 using PubMed. Article selection proceeded according to PRISMA criteria. Studies comparing open adrenalectomy (OA) to LA for ACC and including at least 10 cases per each surgical approach were included. Odds ratio (OR) was used for all binary variables, and weight mean difference (WMD) was used for the continuous parameters. Pooled estimates were calculated with the fixed-effect model, if no significant heterogeneity was identified; alternatively, the random-effect model was used when significant heterogeneity was detected. Main demographics, surgical outcomes, and oncological outcomes were analyzed.
	<i>Results:</i>	Nine studies published between 2010 and 2014 were deemed eligible and included in the analysis, all of them being retrospective case-control studies. Overall, they included 240 LA and 557 OA cases. Tumors treated with laparoscopy were significantly smaller in size (WMD -3.41 cm; confidence interval [CI] -4.91, -1.91; $p < 0.001$ ), and a higher proportion of them (80.8 %) more at a localized (I-II) stage compared with open surgery (67.7 %) (odds ratio [OR] 2.8; CI 1.8, 4.2; $p < 0.001$ ). Hospitalization time was in favor of laparoscopy, with a WMD of -2.5 days (CI -3.3, -1.7; $p < 0.001$ ). There was no difference in the overall recurrence rate between LA and OA (relative risk [RR] 1.09; CI 0.83, 1.43; $p = 0.53$ ), whereas development of peritoneal carcinomatosis was higher for LA (RR 2.39; CI 1.41, 4.04; $p = 0.001$ ). No difference could be found for time to recurrence (WMD -8.2 months; CI -18.2, 1.7; $p = 0.11$ ), as well as for cancer specific mortality (OR 0.68; CI 0.44, 1.05; $p = 0.08$ ).
	<i>Conclusions:</i>	OA should still be considered the standard surgical management of ACC. LA can offer a shorter hospital stay and possibly a faster recovery. Therefore, this minimally invasive approach can certainly play a role in

this setting, but it should be only offered in carefully selected cases to avoid jeopardizing the oncological outcome.

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Footnote Information

On the behalf of Italian Endourological Association (IEA) Research Office and International Translational Research in Uro-Sciences Team (ITRUST).

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## 2 **Open Versus Laparoscopic Adrenalectomy for Adrenocortical** 3 **Carcinoma: A Meta-analysis of Surgical and Oncological** 4 **Outcomes**

5  
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15

### 16 **ABSTRACT**

17 **Purpose.** This study was designed to determine the role of  
18 laparoscopic adrenalectomy (LA) in the surgical manage-  
19 **ment of adrenocortical carcinoma (ACC).**

20 **Methods.** A systematic literature review was performed  
21 on January 2, 2015 using PubMed. Article selection pro-  
22 ceeded according to PRISMA criteria. Studies comparing  
23 open adrenalectomy (OA) to LA for ACC and including at  
24 least 10 cases per each surgical approach were included.  
25 Odds ratio (OR) was used for all binary variables, and  
26 weight mean difference (WMD) was used for the contin-  
27 **uous parameters. Pooled estimates were calculated with the**  
28 **fixed-effect model, if no significant heterogeneity was**  
29 **identified; alternatively, the random-effect model was used**  
30 **when significant heterogeneity was detected. Main demo-**  
31 **graphics, surgical outcomes, and oncological outcomes**  
32 **were analyzed.**

33 **Results.** Nine studies published between 2010 and 2014 were  
34 deemed eligible and included in the analysis, all of them being

retrospective case-control studies. Overall, they included 240  
LA and 557 OA cases. Tumors treated with laparoscopy were  
significantly smaller in size (WMD -3.41 cm; confidence  
interval [CI] -4.91, -1.91;  $p < 0.001$ ), and a higher propor-  
tion of them (80.8 %) more at a localized (I-II) stage compared  
with open surgery (67.7 %) (odds ratio [OR] 2.8; CI 1.8, 4.2;  
 $p < 0.001$ ). Hospitalization time was in favor of laparoscopy,  
with a WMD of -2.5 days (CI -3.3, -1.7;  $p < 0.001$ ). There  
was no difference in the overall recurrence rate between LA  
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(OR 0.68; CI 0.44, 1.05;  $p = 0.08$ ).

**Conclusions.** OA should still be considered the standard  
surgical management of ACC. LA can offer a shorter  
hospital stay and possibly a faster recovery. Therefore, this  
minimally invasive approach can certainly play a role in  
this setting, but it should be only offered in carefully  
selected cases to avoid jeopardizing the oncological  
outcome.

Adrenocortical carcinoma (ACC) represents a rare but  
rather aggressive tumor,<sup>1</sup> often associated with poor  
prognosis, despite aggressive multimodality treatment.<sup>2</sup>  
Surgical resection has traditionally been paying a major  
role in the management of the disease, especially in its  
early stages, where there might still be a window for cure.<sup>3</sup>

A1 On the behalf of Italian Endourological Association (IEA) Research  
A2 Office and International Translational Research in Uro-Sciences  
A3 Team (ITRUST).

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Laparoscopic adrenalectomy was first reported by Gagner et al. 1992 and since then rapidly implemented for the resection of functioning and non functioning adrenal masses, given the recognized advantages in terms of postoperative morbidity and hospital stay compared with open surgery.<sup>4-6</sup> More recently, the role of robot-assisted laparoscopy has been postulated for adrenal surgery.<sup>7</sup>

Laparoscopic surgery for malignant adrenal tumors also has been explored, but its role remains highly debated, given concerns regarding the quality of surgical resection and related oncological risks.<sup>8-10</sup> In case of ACC, several laparoscopic series have been reported, with conflicting results. According to contemporary guidelines open surgery should be regarded as the standard treatment of patients with localized (stage I-II)/locally advanced (stage III) ACC, whereas laparoscopic adrenalectomy can be pursued in selected patients with small ACCs (<8 cm) without preoperative evidence for invasiveness. Moreover, this technique should be ideally performed in centers with a consolidated experience in laparoscopic adrenal surgery.<sup>11,12</sup>

The goal of this study was to provide a systematic review and meta-analysis of available comparative studies assessing laparoscopic adrenalectomy (LA) versus open adrenalectomy (OA) for the surgical resection of ACC.

## METHODS

### Literature Search and Studies Selection

A computerized systematic literature search was performed by using the PubMed database to identify studies published as of January 2, 2015. The following search free text terms were used: “laparoscopic adrenalectomy” OR “adrenocortical carcinoma.” Only studies that meet the following eligibility criteria were included: original study, comparing OA to LA for the specific indication ACC, including at least 10 cases per study group, and allowing data extraction of relevant outcomes. Identification and selection of the studies was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria ([www.prisma-statement.org](http://www.prisma-statement.org)). All titles were screened for manuscripts written in the English language, and only on adult patients. Titles of articles were first reviewed to ascertain whether they might potentially fit the inclusion criteria. After assessing the abstract, a more thorough subsequent assessment was performed by looking at full text.

### Study Quality Assessment

Because none of them was a randomized controlled trial, the methodological quality of the studies was rated according the Newcastle–Ottawa Scale (NOS) for

observational retrospective studies.<sup>13</sup> The level of evidence was reported as described by the Oxford Center for Evidence-Based Medicine.<sup>14</sup>

### Outcomes of Interest

The following relevant parameters were assessed: demographics, including patients’ age, tumor characteristics (clinical presentation, size, stage, Weiss score<sup>15</sup>); surgical outcomes (operative time, postoperative major (Clavien grade >2) complication rate, hospital stay, R0 surgical margins status, use of adjuvant therapy—defined as any form of adjuvant therapy, such as chemotherapy, mitotane, radiation therapy), and oncological outcomes (rate of recurrence—defined as clinical, laboratory, or radiologic evidence of disease recurrence; time to recurrence—defined as the time between surgery and occurrence of disease recurrence; rate of cancer specific mortality—defined as number of deaths, with cancer as the underlying cause of death, occurring in the study population during the follow-up period).

### Statistical Analysis

A meta-analysis of extractable data was performed. Odds ratio (OR) was used for all binary variables, and weight mean difference (WMD) was used for the continuous parameters. For the studies presenting continuous data as means and range, estimated standard deviations were calculated using the methodology described by Hozo et al.<sup>15</sup> Pooled estimates were calculated with the fixed-effect model (Mantel–Haenszel method), if no significant heterogeneity was identified; alternatively, the random-effect model (DerSimonian–Laird method) was used when significant heterogeneity was detected.<sup>16,17</sup> The final pooled effects were reported by the z test, and  $p < 0.05$  was considered as statistically significant. To assess the heterogeneity among the included studies, the Cochrane  $\chi^2$  test and inconsistency ( $I^2$ ) were used. Evaluation of potential publication bias was done by funnel plots analysis for each outcome. The data analysis was performed using the Review Manager software (Revman v.5.2.8, Cochrane Collaboration, Oxford, UK).

## RESULTS

The initial search yielded 2070 and 2566 records, whose 52 titles were screened. After initial screening and removal of duplicates, 24 articles were considered and reviewed based on title and abstract. At the end of the process, nine studies were reviewed in full text and confirmed to meet eligibility criteria (Fig. 1).<sup>18-26</sup>

158 **AQ6** An overview of the studies, all published between 2010  
159 and 2014, is provided in Table 1. Overall, the quality of  
160 studies was high, despite all being retrospective case-  
161 control studies with a low level of evidence.

## 162 Demographics

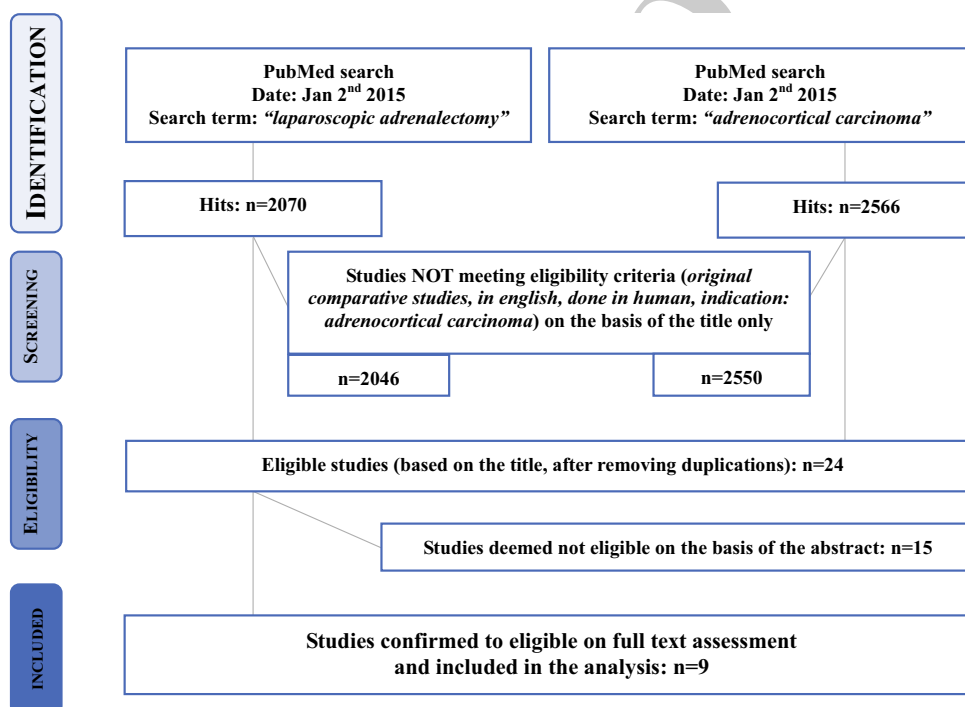
163 Patients undergoing OA were older than those submitted  
164 to LA (WMD 2.56 years; CI 0.78, 4.34;  $p = 0.005$ ). In four  
165 studies the clinical presentation of the adrenal tumor was  
166 described, and a higher rate of incidentalomas was found in  
167 the LA group (43 %) versus the OA group (31.8 %) (OR  
168 2.39; CI 1.39, 4.12;  $p = 0.002$ ).<sup>18,20,21,24</sup> Tumors treated

with laparoscopy were significantly smaller in size (WMD 169  
–3.41 cm; CI –4.91, –1.91;  $p < 0.001$ ), and a higher pro- 170  
portion of them (80.8 %) more at a localized (I–II) stage 171  
compared to open surgery (67.7 %) (OR 2.8; CI 1.8, 4.2; 172  
 $p < 0.001$ ). The Weiss score, which was available in four 173  
studies only, was similar between the two groups (WMD 174  
–0.01, CI –0.27, 0.25;  $p = 0.95$ ).<sup>18,20,23,26</sup> 175

## Surgical Outcomes

Data related to operative time were available for analysis 177  
in three studies, and no difference could be detected between 178  
the two techniques ( $p = 0.85$ ).<sup>21,23,24</sup> EBL was reported in 179

**FIG. 1** PRISMA flow diagram illustrating the study selection process



**TABLE 1** Characteristics and quality assessment of the included studies

Study	Study period	No. of cases (OA:LA)	Tumor stage	Study design	Level of evidence <sup>a</sup>	Quality score <sup>b</sup>
Porpiglia <sup>18</sup>	2002–2008	25:18	I/II only	Retrospective case control	4	8/9
Miller <sup>19</sup>	2003–2008	71:17	I–III	Retrospective case control	4	8/9
Brix <sup>20</sup>	1996–2009	117:35	I–III	Retrospective case control	4	9/9
Lombardi <sup>21</sup>	2003–2010	126:30	I–II	Retrospective case control	4	8/9
Miller <sup>22</sup>	2005–2011	110:46	I–III	Retrospective case control	4	8/9
Mir <sup>23</sup>	1993–2011	26:18	I–IV	Retrospective case control	4	8/9
Fossa <sup>24</sup>	1998–2011	15:17	I–III	Retrospective case control	4	8/9
Cooper <sup>25</sup>	1993–2012	46:46	I–IV	Retrospective case control	4	8/9
Donatini <sup>26</sup>	1985–2011	21:13	I/II only	Retrospective case control	4	8/9

OA open adrenalectomy, LA laparoscopic adrenalectomy

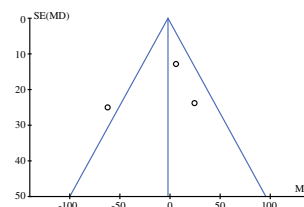
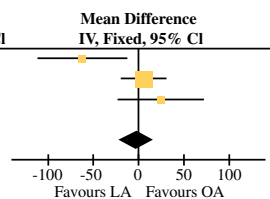
<sup>a</sup> Oxford criteria

<sup>b</sup> Newcastle–Ottawa scale

**a. Operative time**

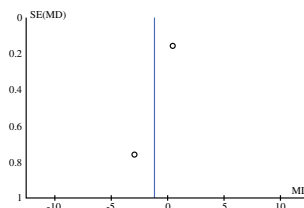
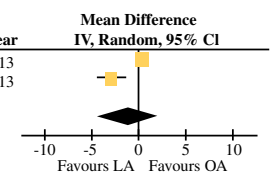
Study or Subgroup	LA			OA			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Fossa 2013	179	87	17	241	52	15	16.9%	-62.00 [-111.02, -12.98]
Lombardi 2012	135	65	30	129	54	126	64.6%	6.00 [-19.10, 31.10]
Mir 2013	297.5	78	18	272.5	78	26	18.5%	25.00 [-21.88, 71.88]
<b>Total (95% CI)</b>			<b>65</b>			<b>167</b>	<b>100.0%</b>	<b>-1.99 [-22.16, 18.17]</b>

Heterogeneity:  $\text{Chi}^2 = 7.42$ ,  $\text{df} = 2$  ( $P = 0.02$ );  $I^2 = 73\%$   
 Test for overall effect:  $Z = 0.19$  ( $P = 0.85$ )

**b. EBL**

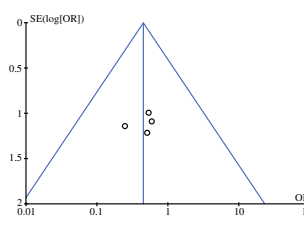
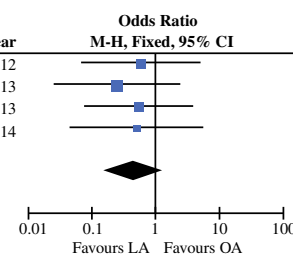
Study or Subgroup	LA			OA			Weight	Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Mir 2013	1.5	0.44	17	1.1	0.61	26	52.5%	0.40 [0.09, 0.71]	2013
Fossa 2013	0.67	0.51	18	3.6	2.9	15	47.5%	-2.93 [-4.42, -1.44]	2013
<b>Total (95% CI)</b>			<b>35</b>			<b>41</b>	<b>100.0%</b>	<b>-1.18 [-4.44, 2.08]</b>	

Heterogeneity:  $\text{Tau}^2 = 5.24$ ,  $\text{Chi}^2 = 18.45$ ,  $\text{df} = 1$  ( $P < 0.0001$ );  $I^2 = 95\%$   
 Test for overall effect:  $Z = 0.71$  ( $P = 0.48$ )

**c. Postoperative complication rate**

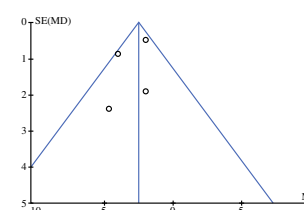
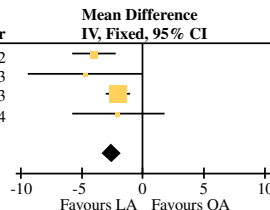
Study or Subgroup	LA		OA		Weight	Odds Ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
Lombardi 2012	1	30	7	126	22.8%	0.59 [0.07, 4.95]	2012
Mir 2013	1	18	5	126	33.9%	0.25 [0.03, 2.32]	2013
Fossa 2013	2	17	3	15	24.7%	0.53 [0.08, 3.72]	2013
Donatini 2014	1	13	3	21	18.6%	0.50 [0.05, 5.39]	2014
<b>Total (95% CI)</b>		<b>78</b>		<b>188</b>	<b>100.0%</b>	<b>0.44 [0.15, 1.30]</b>	

Total events: 5 (LA), 18 (OA)  
 Heterogeneity:  $\text{Chi}^2 = 0.37$ ,  $\text{df} = 3$  ( $P = 0.95$ );  $I^2 = 0\%$   
 Test for overall effect:  $Z = 1.49$  ( $P = 0.14$ )

**d. Hospital stay**

Study or Subgroup	LA			OA			Weight	Mean Difference IV, Fixed, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Lombardi 2012	5.3	3.7	30	9.3	6.2	126	21.7%	-4.00 [-5.71, 2.29]	2012
Fossa 2013	10.5	7.5	17	15.2	6	15	2.9%	-4.70 [-9.38, -0.02]	2013
Mir 2013	4	1.4	18	6	1.8	26	70.8%	-2.00 [-2.95, -1.05]	2013
Donatini 2014	7	5	13	9	6	21	4.5%	-2.00 [-5.74, 1.74]	2014
<b>Total (95% CI)</b>			<b>78</b>			<b>188</b>	<b>100.0%</b>	<b>-2.51 [-3.31, -1.72]</b>	

Heterogeneity:  $\text{Chi}^2 = 4.94$ ,  $\text{df} = 3$  ( $P = 0.18$ );  $I^2 = 39\%$   
 Test for overall effect:  $Z = 6.18$  ( $P < 0.00001$ )

**FIG. 2** Forrest and funnel plots for surgical outcomes

180 two studies only, and no difference could be detected  
 181 ( $p = 0.48$ ; Fig. 2).<sup>23,24</sup> Postoperative complication rate was  
 182 available in four studies, and, again, there was no difference  
 183 between laparoscopy and open surgery ( $p = 0.14$ ).<sup>21,23,24,26</sup>  
 184 In the same four studies, the hospitalization time was reported,  
 185 and this was consistently in favor of laparoscopy, with a  
 186 WMD of  $-2.5$  days (CI  $-3.3, -1.7$ ;  $p < 0.001$ ).<sup>21,23,24,26</sup>  
 187 There was no difference in the rate of negative surgical  
 188 margins (R0), which was reported in seven of the studies  
 189 (61.9 % for LA, 57.6 % for OA;  $p = 0.98$ ).<sup>19,20,22-26</sup> Adjuvant  
 190 therapy was used in a similar proportion of cases for LA  
 191 and OA (32.5 and 29.8 %, respectively;  $p = 0.91$ ).<sup>20,21,23,25</sup>  
 192 The funnel plots suggested no publication bias, so that  
 193 heterogeneity is most likely explained by other differences  
 194 between the studies, such as study design, patient selection,  
 195 and outcome assessment.

**196 Oncological Outcomes**

197 There was no difference in the overall recurrence rate  
 198 between LA and OA (RR 1.09; CI 0.83, 1.43;  $p = 0.53$ ;

Fig. 3).<sup>18-26</sup> In five studies, investigators looked at the  
 development of peritoneal carcinomatosis at the time of  
 recurrence, and there was an overall higher risk for LA  
 versus OA (RR 2.39; CI 1.41, 4.04;  $p = 0.001$ ).<sup>19,20,23-25</sup>

Time to recurrence was reported in four studies only,  
 and, also for this outcome, no significant difference could  
 be detected between LA and OA (WMD  $-8.2$  months; CI  
 $-18.2, 1.7$ ;  $p = 0.11$ ).<sup>19,21-23</sup> Cancer-specific mortality  
 was available for analysis in six of the studies, and, again,  
 no significant difference was found (OR 0.68; CI 0.44,  
 1.05;  $p = 0.08$ ).<sup>18,20,21,23,25, 26</sup> Also for these outcomes,  
 the funnel plots suggested no publication bias, but rather  
 heterogeneity related to other confounders related to study  
 design.

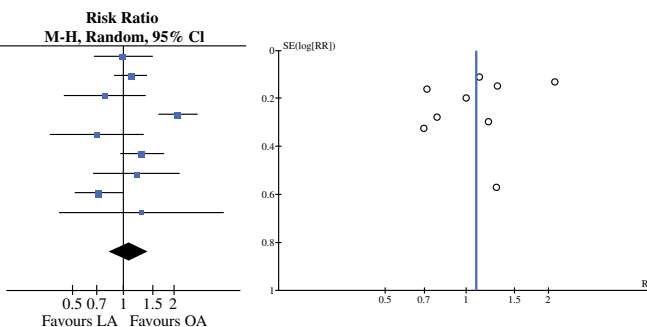
**DISCUSSION**

An appropriate surgical resection is a mandatory step in  
 the therapeutic management of ACC. Thus, the role of  
 minimally invasive surgery for this specific indication is  
 still under scrutiny, as data supporting its implementation

**a. Overall recurrence rate**

Study or Subgroup	LA		OA		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Random, 95% CI	Year	
Miller 2010	11	17	46	71	12.2%	1.00	[0.68, 1.48]	2010
Brix 2010	27	35	81	117	14.8%	1.11	[0.90, 1.38]	2010
Porpiglia 2010	9	18	16	25	9.8%	0.78	[0.45, 1.35]	2010
Miller 2012	39	46	44	110	14.2%	2.12	[1.64, 2.75]	2012
Lombardi 2012	8	30	48	126	8.6%	0.70	[0.37, 1.32]	2012
Cooper 2013	35	46	27	46	13.7%	1.30	[0.97, 1.74]	2013
Mir 2013	10	18	12	26	9.2%	1.20	[0.67, 2.16]	2013
Fossa 2013	12	17	15	15	13.3%	0.72	[0.52, 0.99]	2013
Donatini 2014	4	13	5	21	4.3%	1.29	[0.42, 3.95]	2014
<b>Total (95% CI)</b>		<b>240</b>		<b>557</b>	<b>100.0%</b>	<b>1.09</b>	<b>[0.83, 1.43]</b>	
Total events	155		294					

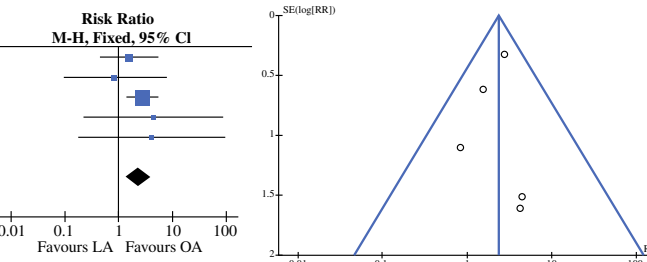
Heterogeneity: Tau<sup>2</sup> = 0.12; Chi<sup>2</sup> = 35.13, df = 8 (P < 0.0001); I<sup>2</sup> = 77%  
 Test for overall effect: Z = 0.63 (P = 0.53)



**b. Peritoneal carcinomatosis at recurrence**

Study or Subgroup	LA		OA		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI	Year	
Miller 2010	3	17	8	71	20.8%	1.57	[0.46, 5.29]	2010
Brix 2010	1	35	4	117	12.4%	0.84	[0.10, 7.24]	2010
Cooper 2013	25	46	9	46	60.5%	2.78	[1.46, 5.28]	2013
Fossa 2013	2	17	0	15	3.6%	4.44	[0.23, 85.83]	2013
Mir 2013	1	18	0	26	2.8%	4.26	[0.18, 99.12]	2013
<b>Total (95% CI)</b>		<b>133</b>		<b>275</b>	<b>100.0%</b>	<b>2.39</b>	<b>[1.41, 4.04]</b>	
Total events	32		21					

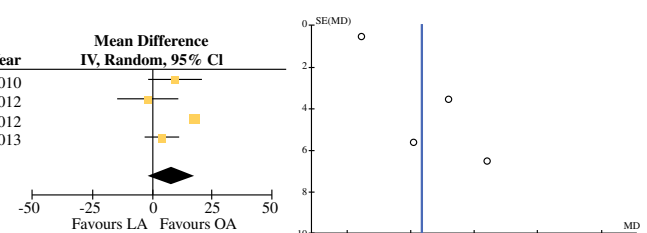
Heterogeneity: Chi<sup>2</sup> = 1.88, df = 4 (P = 0.76); I<sup>2</sup> = 0%  
 Test for overall effect: Z = 3.24 (P = 0.001)



**c. Time to recurrence**

Study or Subgroup	OA		LA		Weight	Mean Difference		Year		
	Mean	SD	Mean	SD		IV, Random, 95% CI	Year			
Miller 2010	19.2	37.5	71	9.6	14	22.4%	9.60	[-1.37, 20.57]	2010	
Lombardi 2012	27	27	126	29	33	20.5%	-2.00	[-14.71, 10.71]	2012	
Miller 2012	29.5	5.2	110	117	2.1	46	30.5%	17.80	[16.65, 18.95]	2012
Mir 2013	13.8	13.8	26	9.7	9.6	18	26.7%	4.10	[-2.81, 11.01]	2013
<b>Total (95% CI)</b>			<b>333</b>		<b>111</b>	<b>100.0%</b>	<b>8.25</b>	<b>[-1.75, 18.26]</b>		

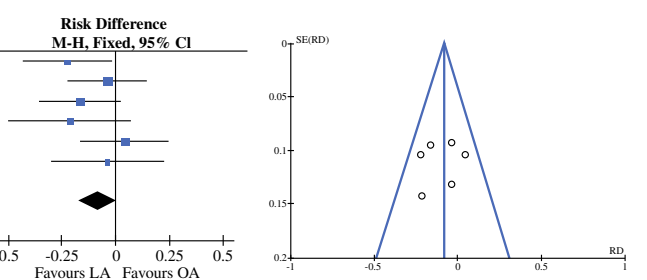
Heterogeneity: Tau<sup>2</sup> = 85.22; Chi<sup>2</sup> = 25.45, df = 3 (P < 0.0001); I<sup>2</sup> = 88%  
 Test for overall effect: Z = 1.62 (P = 0.11)



**d. Cancer specific mortality rate**

Study or Subgroup	LA		OA		Weight	Risk Difference		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI	Year	
Porpiglia 2010	1	18	7	25	10.6%	-0.22	[-0.43, -0.02]	2010
Brix 2010	13	35	48	117	27.3%	-0.04	[-0.22, 0.14]	2010
Lombardi 2012	5	24	41	110	19.9%	-0.16	[-0.35, 0.02]	2012
Mir 2013	10	18	20	26	10.8%	-0.21	[-0.49, 0.07]	2013
Cooper 2013	22	46	20	46	23.3%	0.04	[-0.16, 0.25]	2013
Donatini 2014	2	13	4	21	8.1%	-0.04	[-0.29, 0.22]	2014
<b>Total (95% CI)</b>		<b>154</b>		<b>345</b>	<b>100.0%</b>	<b>-0.08</b>	<b>[-0.17, 0.01]</b>	
Total events	53		140					

Heterogeneity: Chi<sup>2</sup> = 5.22, df = 5 (P = 0.39); I<sup>2</sup> = 4%  
 Test for overall effect: Z = 1.83 (P = 0.07)



**FIG. 3 a, b** Forrest and funnel plots for oncological outcomes

218 remain scanty and controversial outcomes have been  
 219 reported.<sup>12</sup> A recent analysis of the large National Inpatient  
 220 Sample database has suggested that the use of laparoscopic  
 221 techniques to perform adrenalectomy has increased at a  
 222 slower rate over the last decade when compared with other  
 223 procedures.<sup>27</sup>

224 The present systematic review and meta-analysis pro-  
 225 vides the best currently available evidence on the  
 226 comparative outcomes of laparoscopy versus open surgery  
 227 for the surgical resection of ACC with the aim of

228 determining to what extent a minimally invasive approach  
 229 should be considered in this setting.

230 Few findings of our analysis are of worth of consideration.  
 231 First and foremost, the fact that a limited number of com-  
 232 parative studies are available, most of them with a limited  
 233 number of cases, especially for the laparoscopic cohorts,  
 234 which reflects the rarity of the disease. Moreover, despite  
 235 being of good quality, all of these studies are retrospective  
 236 case-control series, implying a patient selection bias and  
 237 other intrinsic limitations related to their design.

238 Nevertheless, the lack of randomized trial is recognized as a  
239 common drawback of clinical investigation for any surgical  
240 specialty. The two largest studies comparing LA to OA are  
241 based on multi-institutional analyses, namely the one  
242 reported by the German Adrenocortical Carcinoma Registry  
243 Group and the one based on an Italian multi-institutional  
244 survey.<sup>20,21</sup> In both studies, the ratio open:laparoscopic cases  
245 was approximately 3:1, which suggest that in these special-  
246 ized centers there has been a selective implementation of  
247 laparoscopy. Both studies concluded that oncologic out-  
248 comes are not jeopardized if proper patient selection is  
249 embraced and principles of oncological radicality are  
250 respected.

251 Not surprisingly, we found that patients undergoing OA  
252 were on approximately 2.5 years older than those submit-  
253 ted to LA ( $p = 0.005$ ). Moreover, tumors treated with LA  
254 are more likely to represent incidental diagnosis  
255 ( $p = 0.002$ ), smaller in size ( $p < 0.001$ ), and a localized  
256 (I–II) stage compared with OA ( $p < 0.001$ ). On the other  
257 hand, in six of the nine comparative studies, cases of  
258 nonlocalized ACC (stage III–IV) were included,<sup>19,20,22–25</sup>  
259 which can reflect the status of referral centers reporting the  
260 studies. Center volume and surgical experience play a  
261 crucial role in the oncologic outcome of patients with  
262 adrenal malignancies; it has been suggested that adrenal  
263 cancer surgery should be performed only in centers with  
264  $>10$  cases per year.<sup>28</sup>

265 No significant differences could be found in terms of  
266 main surgical parameters (operative time, EBL, and com-  
267 plication rate) between LA and OA. The lack of significant  
268 difference in terms of operative time can be regarded as an  
269 unexpected finding especially considering the need for  
270 adjacent organ removal that is very time consuming step,  
271 and it was probably more extensive in the open surgery  
272 cases. To note, the surgical outcome “operative time”  
273 could be retrieved only in one third of the studies included  
274 in the meta-analysis. Thus, there might have certainly been  
275 a case selection bias. In addition, we could not assess in  
276 this setting the impact of the “learning curve” factor. In  
277 other words, the surgical experience of the different sur-  
278 geons from the different studies might have played a role.  
279 Also, when considering that most of these are academic  
280 institutions, one can speculate that residents/fellows were  
281 involved in portions of the cases, thus impacting the  
282 duration of surgery.

283 Hospitalization time was clearly in favor of laparoscopy,  
284 with a statistical ( $p < 0.001$ ) but also clinically significant  
285 difference (WMD of  $-2.5$  days). The concept that  
286 laparoscopic surgery shortens hospital stay and likely  
287 enables a faster return to normal daily activities has been  
288 largely demonstrated for a variety of urologic diseases.<sup>29</sup>

289 The importance of complete, en bloc, margin-negative  
290 resection of ACC in patients who are fit to undergo surgery

291 is a consolidated principle. In a large analysis from the  
292 national cancer database, Bilimoria et al. showed that  
293 median survival for patients with margin-negative resec-  
294 tion was 51.2 months, whereas it was only 7 months for  
295 those who underwent margin positive resection.<sup>30</sup> We  
296 found no difference in the rate of negative surgical mar-  
297 gins, which was reported in seven of the studies (61.9 %  
298 for LA, 57.6 % for OA;  $p = 0.98$ ).<sup>19,20,22–26</sup>

299 The aggressive behavior of ACC provided the rationale  
300 for the use of adjuvant therapy, either radiotherapy to the  
301 tumor bed or mitotane.<sup>31</sup> We found that adjuvant therapy  
302 (any form) was used in a similar proportion of cases for LA  
303 and OA (32.5 and 29.8 %, respectively;  $p = 0.91$ )<sup>20,21,23,25</sup>;  
304 however, this finding is difficult to interpret as different  
305 Centers might have adopted different therapeutic criteria.

306 In the only available meta-analysis of studies comparing  
307 LA versus OA for ACC, Sgourakis et al. looked at the  
308 oncological outcomes for stage I/II disease.<sup>32</sup> They inclu-  
309 ded four comparative studies, all of them also included in  
310 our meta-analysis.<sup>18,21,24,26</sup> The authors found that OA  
311 seems to provide better survival rates at 5 years. This  
312 finding resembles those reported by Miller et al., who  
313 reviewed the single-institution experience with the surgical  
314 treatment of 217 cases of ACC (stage I–III).<sup>19</sup> Overall  
315 survival for patients with stage II cancer was longer in  
316 those undergoing OA. Moreover, time to local or peritoneal  
317 recurrence was shorter in those treated laparoscopically.

318 We could not find differences for most relevant onco-  
319 logical outcomes between LA and OA, namely the overall  
320 recurrence rate ( $p = 0.53$ ), time to recurrence ( $p = 0.11$ ),  
321 and cancer-specific mortality ( $p = 0.08$ ). However, there  
322 was a higher risk of development of peritoneal carcino-  
323 matosis at the time of recurrence for LA (RR 2.39; CI 1.41,  
324 4.04;  $p = 0.001$ ). This finding is in line with the study by  
325 Leboulleux et al., who found the surgical approach to be  
326 related to the risk of peritoneal carcinomatosis,<sup>33</sup> as well as  
327 data reported by Gonzalez et al. who observed peritoneal  
328 carcinomatosis in 5 of the 6 patients (83 %) who under-  
329 went laparoscopic resection of ACC in their series.<sup>10</sup>  
330 Considering that patients with ACC recurrence seem to  
331 have higher survival rates if amenable to complete surgical  
332 resection and the presence of peritoneal recurrence is likely  
333 to compromise a salvage surgery, these findings support the  
334 concept that a complete oncological resection remains the  
335 key factor, and it should not be compromised by the  
336 implementation of a minimally invasive approach.

337 The major limitation of this meta-analysis is related to  
338 the retrospective design of included studies, which allowed  
339 the analysis to be necessarily limited to certain parameters.  
340 Thus, it was not possible to perform a more detailed sep-  
341 arate analysis of oncological outcomes (local recurrence  
342 only versus distant recurrence only versus peritoneal car-  
343 cinomatosis only versus a combination of these events).

344 Similarly, it was not possible to weight the impact of the  
345 different forms of adjuvant therapy used in the different  
346 studies. Moreover, it is not possible to account for existing  
347 differences among centers in terms of surgical techniques,  
348 as well as protocols of perioperative management and  
349 oncological follow-up. Despite these limitations, we are  
350 able to provide the best available evidence in the field, as  
351 nine studies with more than 700 ACC cases were included  
352 in the analysis. Thus, our findings can be used as reference  
353 for further clinical investigation.

354 Last, the role of robot-assisted laparoscopy in this set-  
355 ting remains to be determined. Robot-assisted laparoscopy  
356 is being implemented for adrenal surgery and recent evi-  
357 dence suggests that robotic adrenalectomy can be  
358 performed safely and effectively with potential advantages  
359 of a shorter hospital stay, less blood loss, and lower  
360 occurrence of postoperative complications.<sup>7</sup> Data on the  
361 use of robotics for large adrenal masses remain scanty, but  
362 early series are encouraging.<sup>34</sup>

## 363 CONCLUSIONS

364 OA should be still considered the standard for the sur-  
365 gical management of ACC, as it allows proper radical  
366 extirpation of the disease. LA can offer a shorter hospital  
367 stay, possibly allowing a quicker postoperative recovery,  
368 and it can certainly have a complementary role in this  
369 setting. However, this minimally invasive approach should  
370 be only offered in carefully selected ACC cases and by  
371 centers with appropriate laparoscopic expertise in order to  
372 avoid jeopardizing the oncological outcome.

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